# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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# PCT

## WRITTEN OPINION
(PCT Rule 66)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 31.03.2004 |
| Applicant's or agent's file reference: SOPC/P28436PC | **REPLY DUE** within **3 month(s)** from the above date of mailing |
| International application No.: PCT/GB 03/02459 | International filing date *(day/month/year)*: 06.06.2003 |
| Priority date *(day/month/year)*: 07.06.2002 | |
| International Patent Classification (IPC) or both national classification and IPC: C12N15/10 | |
| Applicant: SOPHION BIOSCIENCE A/S et al. | |

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   **When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   **How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   **Also:** For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

   **If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.**
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07.10.2004

Name and mailing address of the international preliminary examining authority:
European Patent Office - P.B. 5818 Patentlaan 2
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## WRITTEN OPINION

International application No. PCT/GB 03/02459

I. **Basis of the opinion**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

**Description, Pages**

1-26 as originally filed

**Claims, Numbers**

1-15 as originally filed

**Drawings, Sheets**

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

## WRITTEN OPINION

International application No. PCT/GB 03/02459

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 5-complete, (6-15)-partially

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 5-complete, (6-15)-partially

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims | 1-4,6-15 |
| Inventive step (IS) | Claims | 1-4,6-15 |
| Industrial applicability (IA) | Claims | |

2. Citations and explanations

**see separate sheet**

**WRITTEN OPINION**
**SEPARATE SHEET**

International application No. PCT/GB03/02459

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims: 5-complete, (6-15)-partially relate to subject-matter (.... **storing and recording** the sequence information on an information carrier, such as a computer disk) not required to be searched by this Authority , Rule 39.1(v) PCT. Therefore no International Search Report was established for claim 5 under Art. 17(2)(a) PCT.

Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability of the subject-matter of this claim (Rule 66.1(e), PCT).

Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 02 24862 A (SCHMIDT CHRISTIAN ;CYTION S A (CH)) 28 March 2002 (2002-03-28)
D2: WO 02 04943 A (SQUIBB BRISTOL MYERS CO) 17 January 2002 (2002-01-17)
D3: WO 99 64582 A (INTROGENE BV) 16 December 1999 (1999-12-16)
D4: WO 01 73000 A (MAXYGEN INC ;KEENAN ROBERT J (US); MINSHULL JEREMY (US); STEMMER W) 4 October 2001 (2001-10-04)
D5: EP 1 143 013 A (WARNER LAMBERT CO) 10 October 2001 (2001-10-10)

1. Clarity (Art. 6 PCT)

1.1 Concerning the objections made for clarity, Art. 6 PCT requires among other things

that the claims, which define the matter for which protection is sought to be clear. This has to be interpreted as meaning not only that a claim from the technical point of view must be comprehensible, but that it must define clearly the object of the invention, that is to say indicate all the essential technical features, which are necessary to obtain the desired effect or, differentially expressed, which are necessary to solve the technical problem with which the application is concerned without undue experimentation.

1.2 Since claim 1 does not contain any essential technical feature it does not meet the requirement following Article 6 PCT.

## 2. Sufficiency of Disclosure (Art. 6 PCT)

The present application does not fulfil the requirements of Art. 6 PCT. The present application does not disclose a single working example of the claimed methods for screening a DNA library nor does the Application disclose a single method wherein the cell is treated with a test agent before using it in said method. The description refers only to known vectors, genes, cells, methods, apparatuses and measurements that could for example be used to screen and perform the electrophysiological measurements but the Application does not work out how at least one DNA library could have been subjected to the methods of the present application.

## 3. Novelty (Art. 33(2) PCT)

3.1 D1 describes a multiaperture **biochip** comprises a substrate including several apertures, a recording fluid compartment and one reference fluid compartment arranged on each side of the substrate and being in contact through the apertures, a recording electrode and a reference electrode in contact with one of the compartments and adapted to measure and/or apply an electrical potential across the apertures. The biochip is useful for positioning and/or analysing samples such as cells, vesicles, cellular organelles, and fragments, derivatives, and their mixtures (claimed), for electrical and/or optical analysis, especially relating to the presence and/or activity of ion channels. The system is useful for automated and/or **high-throughput patch-clamp analysis** (e.g. for drug screening), portable biosensor analysis (e.g. for environmental analytes) and also for separation of cells and vesicles, the analysis of

the sizes of cells or vesicles, the direct functional analysis of ionotropic membrane proteins, for e.g. in ligand binding studies, and/or the positioning of cells or vesicles for any suitable purpose, including optical investigations and/or microinjections. The system is useful in a method to screen libraries including compound, combinatorial chemistry, **gene and phage libraries** for the identification of candidate drugs and modulators and is well suited for probing libraries whose members are present only in small amounts.

3.1.1 In the light of D1, the subject-matter of claims 1-4 and 6-15 is not novel under Art. 33(2) PCT.

## 4. Inventive step (Art. 33(3) PCT)

4.1 **D2** describes an **apparatus** for measuring cellular electrical conditions comprising a cell support membrane component (CSC) adapted to hold one or more cells. Said apparatus is useful for measuring cellular electrical condition such as transmembrane potential, capacitance, resistance and conductance of cells such as human embryonic kidney (HEK)-293 cells, Chinese hamster ovary cells, primary neuronal cells (preferably hippocampus, dorsal root ganglia or superior cervical ganglia cells), skeletal muscle cells, smooth muscle cells, cardiac muscle cells, immune cells, epithelial cells, or endothelial cells. Optionally, said apparatus is useful for **measuring electrical condition** of cells comprising DNA constructs directing the expression of molecules such as ion channel proteins, ion transporters, G-proteins, G-protein receptors, protein kinases or protein phosphatases, cells expressing ion channels that are specific for ions such as sodium, potassium, calcium or chloride. Moreover said apparatus is useful in a **high throughput screening method** for detecting and assaying test agents that affect cellular electrical activity. The test agents which are assayed are e.g. G-proteins and/or G-protein receptors.

**D2**, regarded as the closest state of the art, differs from the subject-matter that it lacks the essential technical feature of describing a method using said apparatus for screening a DNA library. In the light of the prior art the problem of underlying application is the provision of an alternative method for screening a DNA library. The solution as provided by the applicant comprises: (i) providing a substrate for making electrophysiological measurements which at least one cell can be arranged; (ii)

providing at least one cell which expresses at least one heterologous DNA sequence; (iii) arranging at least one cell on the substrate to permit detection and/or measurements of a change in the electrophysiology of the cell; and (iv) identifying at least one cell of interest which shows at least one phenotypic change.

**D3** describes a library of expressible nucleic acids which contains many compartments, each comprising at least one vehicle comprising at least one nucleic acid, the vehicle being capable of efficiently introducing a nucleic acid into a cell for expression. Said library is useful for determining the function of one or more nucleic acids within the library, or to screen for an expressible nucleic acid with a particular desired function. It is especially useful for high throughput screening of gene function for functional genomics applications and for screening for nucleic acids with potential therapeutic value.

**D4** describes a method for controlling, a phenotype which comprises recombining or mutating a population of conjoint polynucleotide segments. Said method further comprises to encode or modulate a phenotype, to produce a library, introducing the library into a population of recipient cells or intracellular organelles and identifying a cell, organelle, or organism comprising a cell with a desired phenotype.

**D5** describes the screening modulators of calcium channel (specifically calcium-release-activated channel (Icrac)) activity by: (a) contacting the modulators and a Ca channel activator with a population of Ca channel expressing cells containing a reporter construct with a reporter gene under the control of a nuclear factor of activated T cells (NFAT)-inducible promoter; and (b) determining the activity of (I) on the channel.

For a man skilled in the art it would be obvious to combine the technical feature of **D2** with any one of **D3-D5** to achieve the same result as in the present application.

4.1.1 In the light of **D2** in combination with any one of **D3 to D5** the subject-matter of claim 1 lack an inventive step under Art. 33(3) PCT.

4.2 The dependent claims 2-4,6-15, merely describes obvious nucleic acid constructs and known technical features, that a man skilled in the art would use to screen DNA libraries. It does not appear to contain any additional features which, in combination with the features of any claim to which they refer, could be taken as constituting to an

inventive step, as the relevant subject-matter falls within the knowledge and ability of the skilled person. For this reason claim 2-4,6-15 does not involve an inventive step and is not allowable under Art. 33(3) PCT.

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD
GRANDE BRETAGNE

11 AUG 2004

PARTNER

# PCT

## WRITTEN OPINION
(PCT Rule 66)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 10.08.2004 |
| Applicant's or agent's file reference: SOPC/P28436PC | REPLY DUE: **within 1 month(s)** from the above date of mailing |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/GB 03/02459 | 06.06.2003 | 07.06.2002 |

International Patent Classification (IPC) or both national classification and IPC
C12N15/10

Applicant
SOPHION BIOSCIENCE A/S et al.

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

| | | |
|---|---|---|
| I | ☒ | Basis of the opinion |
| II | ☐ | Priority |
| III | ☒ | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| IV | ☐ | Lack of unity of invention |
| V | ☒ | Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| VI | ☐ | Certain documents cited |
| VII | ☐ | Certain defects in the international application |
| VIII | ☐ | Certain observations on the international application |

3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed,** the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07.10.2004

Name and mailing address of the international preliminary examining authority:
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NL-2280 HV Rijswijk - Pays Bas
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**WRITTEN OPINION** International application No. PCT/GB 03/02459

I. **Basis of the opinion**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

**Description, Pages**

1-26 as originally filed

**Claims, Numbers**

1-13 received on 26.07.2004 with letter of 23.07.2004

**Drawings, Sheets**

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 14,15
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

**WRITTEN OPINION** International application No. PCT/GB 03/02459

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3-completely (4-13)-partially

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3-complete, (4-13)-partially

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims | |
| Inventive step (IS) | Claims | 1,2,4-13 |
| Industrial applicability (IA) | Claims | |

2. Citations and explanations

**see separate sheet**

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/GB 03/02459

RE Item I

The amended claims 1-13 filed with the letter dated 23.07.2004 and received on 26.07.2004 are allowable according to Art. 34 (2)(b) PCT. The basis of the report issues on the claims as amended according to Rule 70.2 PCT.

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims: 3-completely and (4-13)-partially relate to subject-matter (.... **storing and recording** the sequence information on an information carrier, such as a computer disk) not required to be searched by this Authority , Rule 39.1(v) PCT. Therefore no International Search Report was established for claim 3 under Art. 17(2)(a) PCT.

Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability of the subject-matter of this claim (Rule 66.1(e), PCT).

Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 02 24862 A (SCHMIDT CHRISTIAN ;CYTION S A (CH)) 28 March 2002 (2002-03-28)
D2: WO 02 04943 A (SQUIBB BRISTOL MYERS CO) 17 January 2002 (2002-01-17)
D3: WO 99 64582 A (INTROGENE BV) 16 December 1999 (1999-12-16)
D4: WO 01 73000 A (MAXYGEN INC ;KEENAN ROBERT J (US); MINSHULL JEREMY (US); STEMMER W) 4 October 2001 (2001-10-04)
D5: EP 1 143 013 A (WARNER LAMBERT CO) 10 October 2001 (2001-10-10)

The document D6 was not cited in the international search report. A copy of the document is appended hereto.

D6: R. GEHWOLF ET AL.: 'FIRST PATCH, THEN CATCH: MEASURING THE ACTIVITY AND THE mRNA TRANSCRIPTS OF A PROTON PUMP IN INDIVIDUAL LILIUM POLLEN PROTOPLASTS', FEBS LETTERS, VOL. 512, PAGES 152-156, 13 FEBRUARY 2002, (2002-02-13);

## 1. Clarity (Art. 6 PCT)

1.1 Concerning the objections made for clarity, Art. 6 PCT requires among other things that the claims, which define the matter for which protection is sought to be clear. This has to be interpreted as meaning not only that a claim from the technical point of view must be comprehensible, but that it must define clearly the object of the invention, that is to say indicate all the essential technical features, which are necessary to obtain the desired effect or, differentially expressed, which are necessary to solve the technical problem with which the application is concerned without undue experimentation.

1.2 Since claim 1 does not contain any essential technical feature it does not meet the requirement following Article 6 PCT.

## 2. Novelty (Art. 33(2) PCT)

2.1 D1 describes a multiaperture **biochip** comprises a substrate including several apertures, a recording fluid compartment and one reference fluid compartment arranged on each side of the substrate and being in contact through the apertures, a recording electrode and a reference electrode in contact with one of the compartments and adapted to measure and/or apply an electrical potential across the apertures. The biochip is useful for positioning and/or analysing samples such as cells, vesicles, cellular organelles, and fragments, derivatives, and their mixtures (claimed), for electrical and/or optical analysis, especially relating to the presence and/or activity of ion channels. The system is useful for automated and/or **high-throughput patch-clamp analysis** (e.g. for drug screening), portable biosensor analysis (e.g. for environmental analytes) and also for separation of cells and vesicles, the analysis of the sizes of cells or vesicles, the direct functional analysis of ionotropic membrane

proteins, for e.g. in ligand binding studies, and/or the positioning of cells or vesicles for any suitable purpose, including optical investigations and/or microinjections. The system is useful in a method to screen libraries including compound, combinatorial chemistry, **gene and phage libraries** for the identification of candidate drugs and modulators and is well suited for probing libraries whose members are present only in small amounts.

2.2 **D6** describes a method "First patch, then catch" and measures the activity and the mRNA transcripts of a proton pump in individual Lilium pollen protoplasts. Combining the patch-clamp method with single-cell reverse transcription polymerase chain reaction (scRT-PCR) a fusicoccin-induced current reflecting the activity of the plasma membrane H+ ATPase of lily pollen protoplasts was measured and subsequently, the ATPase-encoding mRNAs were collected and amplified.

2.3 In the light of **D1**and **D6**, the subject-matter of claims 1,2 and 4-13 appears to be new under Art. 33(2) PCT.

## 3. Inventive step (Art. 33(3) PCT)

3.1 Methods to perform an electrophysiological measurement in the manner to isolate a single cell of interest and to isolate mRNA from that single cell of interest respectively methods to combine patch clamp technology with a method to carry out single cell PCR (polymerase chain reaction) is already well known in the prior art.

**D6** describes the combination of the patch-clamp method with single-cell reverse transcription polymerase chain reaction (scRT-PCR). A fusicoccin-induced current reflecting the activity of the plasma membrane H+ ATPase of lily pollen protoplasts was measured and subsequently, the ATPase-encoding mRNAs were collected and amplified. By reconsidering the application and the amended claims, After considering the amended claims, **D6** is regarded as the closest state of the art and differs from the subject-matter that it lacks the technical feature of isolating the cell **expressing at least one heterologous DNA sequences** of interest/or genetic material therefrom, and isolating mRNA from said cell of interest identified. In the light of the prior art the problem of underlying application is the provision of an alternative method for detection and isolation of **heterologous DNA sequences**. The solution as provided by the applicant is a method for performing electrophysiological measurements comprising the step of: (I) providing a substrate for making the electrophysiological measurements

upon which at least one cell can be arranged; (ii) providing at least one cell which expresses at least one heterologous DNA sequence; (iii) arranging at least one cell on the substrate to permit detection and/or measurements of a change in the electrophysiology of the cell; and (iv) identifying at least one cell of interest which shows at least one phenotypic change, characterized in that, the method comprises the further steps of : isolating the cell of interest/or genetic material therefrom; and isolating mRNA from the cell of interest identified in step (ii).

D2 describes an **apparatus** for measuring cellular electrical conditions comprising a cell support membrane component (CSC) adapted to hold one or more cells. Said apparatus is useful for measuring cellular electrical condition such as transmembrane potential, capacitance, resistance and conductance of cells such as human embryonic kidney (HEK)-293 cells, Chinese hamster ovary cells, primary neuronal cells (preferably hippocampus, dorsal root ganglia or superior cervical ganglia cells), skeletal muscle cells, smooth muscle cells, cardiac muscle cells, immune cells, epithelial cells, or endothelial cells. Optionally, said apparatus is useful for **measuring electrical condition** of cells comprising DNA constructs directing the expression of molecules such as ion channel proteins, ion transporters, G-proteins, G-protein receptors, protein kinases or protein phosphatases, cells expressing ion channels that are specific for ions such as sodium, potassium, calcium or chloride. Moreover said apparatus is useful in a **high throughput screening method** for detecting and assaying test agents that affect cellular electrical activity. The test agents which are assayed are e.g. G-proteins and/or G-protein receptors.

D3 describes a library of expressible nucleic acids which contains many compartments, each comprising at least one vehicle comprising at least one nucleic acid, the vehicle being capable of efficiently introducing a nucleic acid into a cell for expression. Said library is useful for determining the function of one or more nucleic acids within the library, or to screen for an expressible nucleic acid with a particular desired function. It is especially useful for high throughput screening of gene function for functional genomics applications and for screening for nucleic acids with potential therapeutic value.

D4 describes a method for controlling, a phenotype which comprises recombining or mutating a population of conjoint polynucleotide segments. Said method further comprises to encode or modulate a phenotype, to produce a library, introducing the library into a population of recipient cells or intracellular organelles and identifying a cell, organelle, or organism comprising a cell with a desired phenotype.

**D5** describes the screening modulators of calcium channel (specifically calcium-release-activated channel (Icrac)) activity by: (a) contacting the modulators and a Ca channel activator with a population of Ca channel expressing cells containing a reporter construct with a reporter gene under the control of a nuclear factor of activated T cells (NFAT)-inducible promoter; and (b) determining the activity of (I) on the channel.

For a man skilled in the art it would be obvious to combine the technical feature of **D6** with any one of **D2-D5** to achieve the same result as in the present application.

3.1.1 In the light of D6 in combination with any one of D2-D5 the subject-matter of claim 1 lack an inventive step under Art. 33(3) PCT.

3.2 The dependent claims 2,4-13, merely describes obvious nucleic acid constructs and known technical features, that a man skilled in the art would use to screen DNA libraries. It does not appear to contain any additional features which, in combination with the features of any claim to which they refer, could be taken as constituting to an inventive step, as the relevant subject-matter falls within the knowledge and ability of the skilled person. For this reason claim 2,4-13 does not involve an inventive step and is not allowable under Art. 33(3) PCT.